



Docket No.: CDJ-166CPRCE  
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:  
Yashwant M. Deo *et al.*

Application No.: 10/035,637

Confirmation No.: 4452

Filed: November 7, 2001

Art Unit: 1644

For: MOLECULAR CONJUGATES COMPRISING  
HUMAN MONOCLONAL ANTIBODIES TO  
DENDRITIC CELLS (as amended)

Examiner: Ewoldt, Gerald R.

**DECLARATION BY DR. TIBOR KELER UNDER 37 C.F.R. §1.132**

MS Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Dr. Tibor Keler, declare the following:

1. I am presently Vice President and Chief Scientific Officer of Celldex Therapeutics Inc. located in Phillipsburg, New Jersey, the assignee of the above-referenced patent application. I received a Ph.D. in microbiology from the University of Pennsylvania and completed a Post-Doctoral Fellowship at Fox-Chase Cancer Center in Philadelphia, Pennsylvania. My *curriculum vitae* is attached herewith as Appendix A.
2. I understand that the presently pending claims of the above-referenced application are drawn to vaccine conjugates comprising a human monoclonal antibody that binds to the human macrophage mannose receptor, linked to an antigen.
3. The purpose of this declaration is to provide the basis for my belief that the claimed invention would not have been obvious to one of ordinary skill in the art at the time the present application was filed in view of the mechanisms that were known about how the macrophage mannose receptor internalizes, processes and presents antigens, which would not have been thought suitable for developing antibody-based vaccines. Therefore, there would not have been motivation to have made the presently claimed molecular conjugates comprising a human monoclonal antibody that binds to the human macrophage mannose receptor, linked to an antigen.
4. It was well-known in the art at the time of filing that dendritic cells are specialized cells of the immune system and are the principal antigen presenting cells involved in primary immune responses. Their major function is to obtain antigen in tissues, migrate to lymphoid organs and activate T cells. Dendritic cells are capable

of evolving from immature, antigen-capturing cells to mature, antigen-presenting, T cell-priming cells; converting antigens into immunogens and expressing molecules such as cytokines, chemokines, costimulatory molecules and proteases to initiate an immune response.

5. As confirmed by Sallusto *et al.* (cited by the Examiner), immature monocyte-derived dendritic cells can efficiently capture and internalize mannosylated antigens and selected other carbohydrate containing ligands via the mannose receptor. Importantly, to accomplish this task, Sallusto *et al.* cite the following two critical characteristics of the mannose receptor to function in antigen presentation: “broad ligand specificity and the capacity to release ligands at low pH”. Specifically, the authors focus on the fact that carbohydrate (*e.g.*, mannosylated antigen) interactions with the carbohydrate binding regions of the mannose receptor are low affinity interactions that are sufficiently strong enough to mediate selective binding, but weak enough to allow efficient dissociation of the ligands and antigens in the intracellular compartments.

6. In contrast, monoclonal antibodies were known in the art to bind target epitopes (*e.g.*, target receptors) with high affinity namely, affinities far greater than the carbohydrate interactions between mannosylated antigens and the mannose receptor. This level of binding would not have been thought suitable for targeting antigens to the mannose receptor, since it would have been expected that the antibody – antigen conjugate would fail to dissociate from the receptor once internalized. This would have applied even to antibodies having low binding affinities, since such affinities are still significantly greater than carbohydrate interactions. Indeed, antibodies which bind the human mannose receptor would not have been expected to exhibit the specialized multivalent properties of mannose receptor ligands necessary for antigen presentation, *i.e.*, such antibodies would not have been expected to exhibit low affinity interactions capable of efficient dissociation of the ligands and antigens in the intracellular compartments. In fact, antibodies to the mannose receptor have been shown to block antigen uptake as described by Sallusto *et al.* (1995), suggesting that this approach may interfere with internalization or receptor multimerization. Moreover, there is no evidence that I am aware of that low affinity antibodies would allow for efficient binding to cellular targets in tissues such as lymph nodes. Antibodies with moderate to good binding affinity would still have higher affinity than most carbohydrate based interactions, as the latter are generally efficiently blocked using antibodies specific for the receptor. Accordingly, therefore, there was no motivation or reasonable expectation of success at the time the present application was filed to have tried using antibodies directed to the mannose receptor to target antigens to dendritic cells for efficient antigen uptake and presentation, or for any other purpose whatsoever. Indeed, this is evidenced by the fact that mannose-mediated uptake of antigens had been known in the art since the early 1990’s, yet no one in the art had tried using antibodies directed to the mannose receptor, in place of mannose receptor ligands, to mediate uptake of antigens.

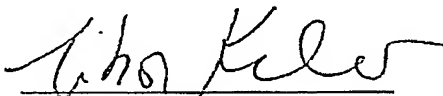
7. Moreover, Sallusto *et al.* make a clear distinction between mannose receptor-mediated endocytosis of ligands and Fc receptor-mediated internalization of ligands, the latter of which results in delivery to lysosomes and the degradation of both the ligand and the receptor. Accordingly, one of ordinary skill would not have been motivated to have used antibodies to target antigens to dendritic cells via the mannose receptor, since such antibodies would have been expected to also inherently bind to the Fc receptors expressed on these cells via their constant regions, thus, resulting in degradation of the ligand and the receptor.

8. The second mechanism of antigen uptake is macropinocytosis. Specifically, macropinocytosis in dendritic cells allows continuous capture of macrosolutes present in the fluid phase. The macrosolutes that are taken up in the fluid phase accumulate with time in the endocytic compartment, where they are loaded on newly synthesized and recycling MHC class II molecules, but may also be released into the cytosol where they become accessible to the class I antigen presentation pathway. Again, such mechanisms for capturing antigens are far different from antibody-mediated antigen presentation, and would not have been thought suitable for antibody-based vaccines.

9. Indeed, prior to the present invention, the mannose receptor was not recognized to capture and process antigens via antibodies. In fact, the anti-mannose receptor antibodies developed by me and my co-inventors as part of the present invention were initially selected by us based on their superior functional properties (e.g., efficient internalization and antigen presentation) before it was known what specific receptor on dendritic cells the antibodies bound to. It was entirely unexpected when the antibodies were later characterized as binding to the human mannose receptor. Moreover, the antibody-mediated internalization that we observed using the presently claimed anti-mannose receptor antibodies was found to involve mechanisms which were entirely different and independent of those involved in model mannose receptor ligand internalization (see, V. Ramakrishna *et al.* (2004) *J. Immunol.* 2846-2852).

10. In conclusion, based at least on the foregoing, because at the time of the present invention it was understood that antigens were presented via the mannose receptor by mechanisms which greatly differed from antibody-targeted mechanisms and would not have been thought suitable for developing antibody-based vaccines, there would not have been motivation to have made the presently claimed molecular conjugates comprising a human monoclonal antibody that binds to the human macrophage mannose receptor linked to an antigen. Importantly, it was not until our invention that antibodies to the human macrophage mannose receptor were unexpectedly discovered to be useful for antigen presentation.

11. I have been warned that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 or the United States Code, and that such willful and false statements may jeopardize the validity of the subject application or any patent resulting therefrom, and declare that all statements made of our own knowledge are true and that all statements made on information and belief are believed to be true.

By: 

Date: Nov. 22, 2006